IND Submissions

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Regulatory Aspects of TB Vaccine Development
Rockville, MD
December 9, 2003

Objectives

- Review the statutory authority for CBER regulation of vaccines and applicable regulations.
- Review early opportunities for TB vaccine developers to interact with CBER.
- Review the procedures for requesting and conducting a pre-IND meeting.
- Review the content & format of INDs.
- Review clinical holds.
- Discuss common IND pitfalls.

CBER Regulation of Vaccines

- Vaccines for human use
- Per authority of:
  - Biologics Control Act (1902)
  - Public Health Service Act, Section 351 (1944)
  - Federal Food, Drug and Cosmetic Act (1938)
- FDA enforces these acts by issuing regulations
  - Title 21 of the Code of Federal Regulations (CFR)

21 Code of Federal Regulations

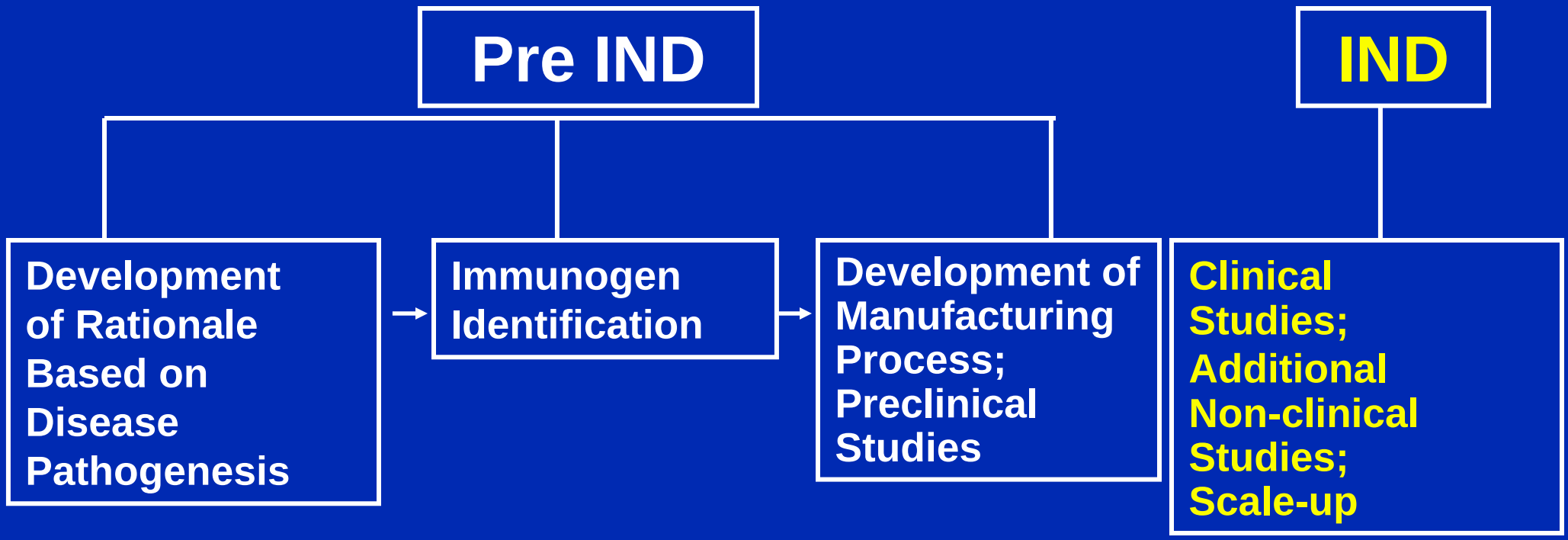
Part 600-680	Biologics
Part 312	INDs
Part 314.126	Adequate & Well-controlled Studies
Part 50	Informed Consent
Part 56	Institutional Review Boards
Part 210, 211	cGMPs
Part 58	GLP-Nonclinical Lab Studies
Part 800	*in vitro* diagnostics

Internet access to the CFR:
http://www.gpoaccess.gov/cfr/index.html

CBER-Regulated Vaccines Must Be…

- Safe (21 CFR 600.3)
  - Relative freedom from harmful effect when prudently administered...
- Pure (21 CFR 600.3)
  - Relative freedom from extraneous matter in the finished product...
- Potent (21 CFR 600.3)
  - Specific ability … to effect a given result.
- Manufactured consistently according to current Good Manufacturing Practices (21 CFR 210-211).

Vaccine Development



IND = Investigational New Drug application

CBER Review

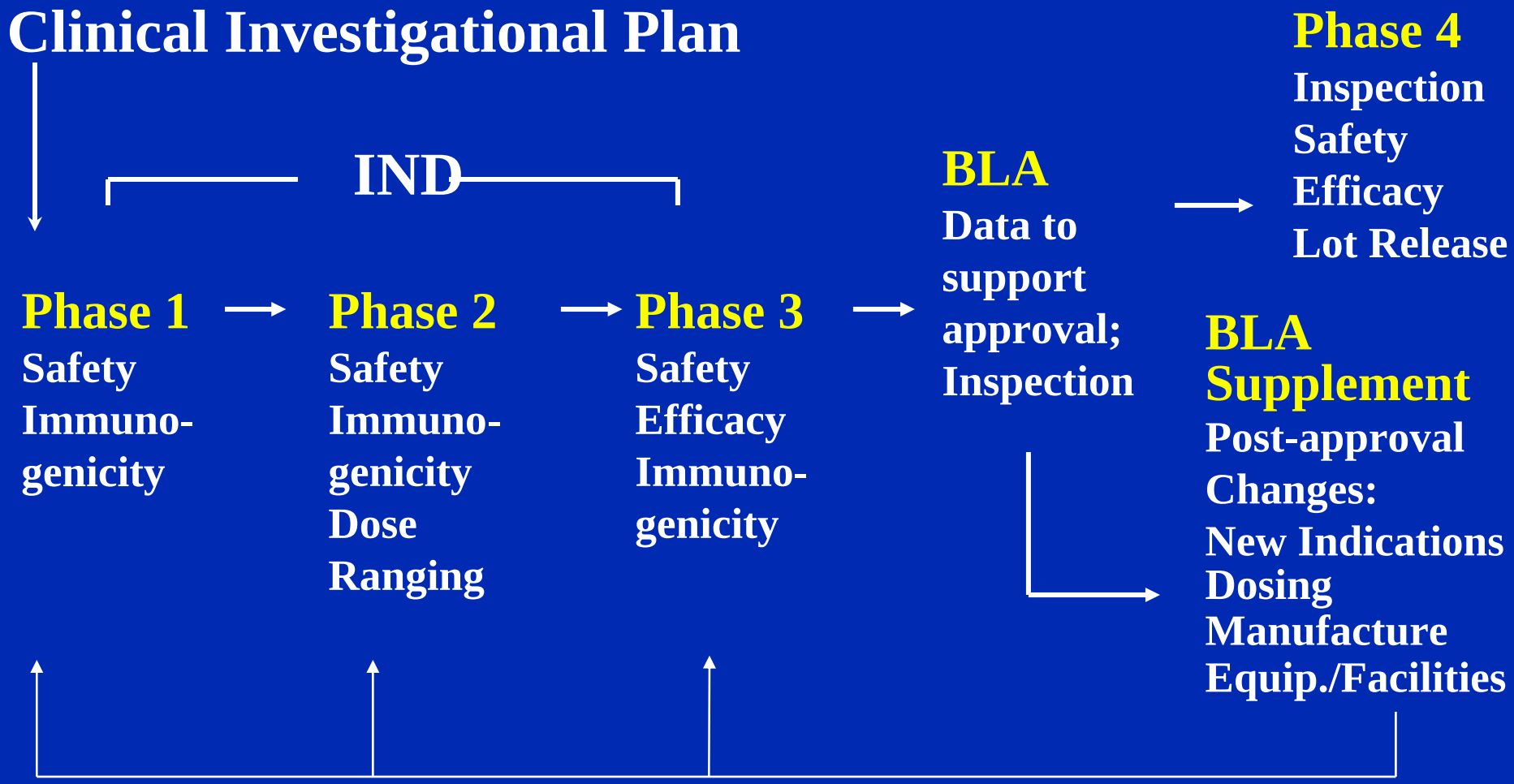
New Biological Product

New Indication for Already Approved Product

Thorough evaluation of scientific and clinical data submitted by sponsors to determine whether the product meets CBER's standards for approval.

CBER makes a decision based on the risk-benefit for the intended population and the product's intended use.

Stages of Review and Regulation



IND =Investigational New Drug Application; BLA=Biologics License Application

General Principles of the IND Submission

- **Scope [21 CFR 312.1]**
  - **Allows an investigational new drug to be lawfully shipped across state lines for the purpose of conducting a clinical study of that drug.**
- **FDA's Review Objectives [21 CFR 312.22]**
  - **In all phase of the investigation, to assure the safety and rights of subjects.**
  - **In Phase 1 investigations, to assess the safety.**
  - **In Phase 2 and 3, to help assure that the quality of the scientific evaluation of drugs is adequate to permit an evaluation of the drug's effectiveness and safety**

Early Dialogue with CBER

- Long before a pre-IND meeting
- Possible and encouraged
- Via teleconference, scientific meeting or outreach presentation
- Focused technical discussion
  - General design of pharm/tox studies
  - Product assays
  - Product characterization
- Unofficial review of informally submitted materials (i.e., faxed one-pager)
- Preliminary, non-binding advice
- Time and resource dependent

Pre-IND Meeting

- Interface between pre-IND and IND phases
- “Dress rehearsal”
- An opportunity to discuss and identify:
  - Product safety issues
  - Design of animal studies needed to initiate human testing
  - Potential clinical hold issues.
- Type B Meeting per PDUFA 2
  - Written request to OVRR/DVRPA (fax or mail)
  - Request should provide adequate information
  - CBER must respond to request within 14 days
  - Scheduled to occur within 60 days of receipt of request
  - In general, only ONE pre-IND meeting granted

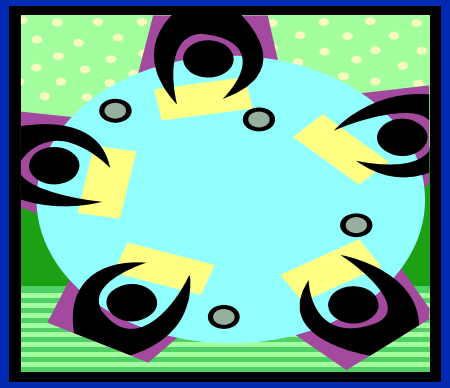
Pre-IND Meeting Pre-read

- Submit at least 4 weeks prior to meeting
- Contents should include (not be limited to):
  - Purpose
  - Objectives
  - Product description
  - Proposed indication
  - Questions for CBER
  - List of sponsor participants
  - Supporting data summaries (CMC, preclinical, clinical)
  - Protocol summary or draft
  - Reprints of key references
- Guidance for Industry:
  - Formal Meetings With Sponsors and Applicants for PDUFA Products (3/7/2000)
  - at http://www.fda.gov/cber/guidelines.htm

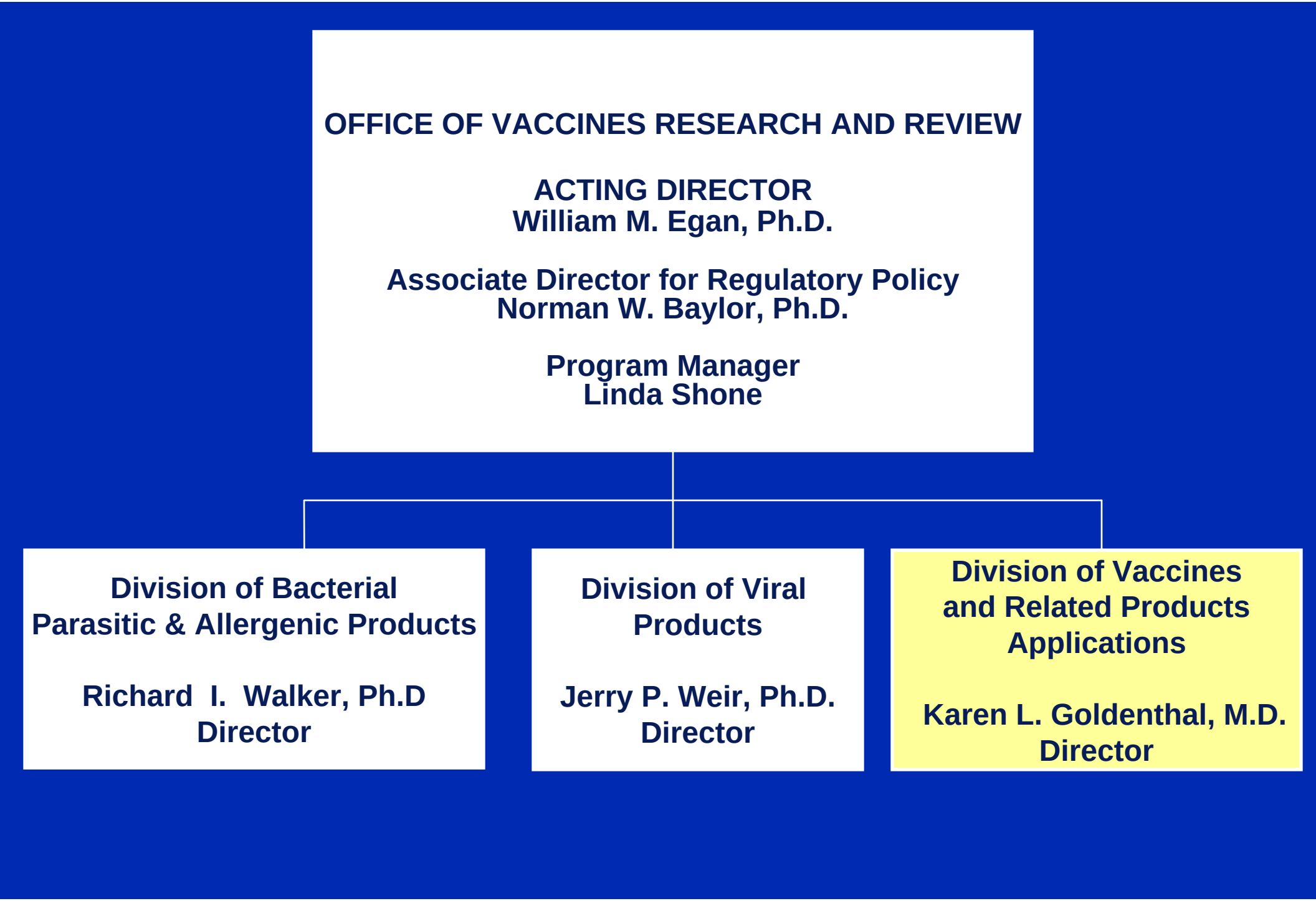
Advice for a Successful Pre-IND Meeting:

- **Submit a complete background package (pre-read) that adequately represents the data to be provided in the IND.**
- **Limit the pre-IND meeting agenda to the issues and immediate questions for CBER.**
- **Issues and questions for CBER should primarily concern how best to proceed into clinical trials.**

The CBER/OVRR IND Review Team



- Primary Reviewer / Regulatory Project Manager (DVRPA)
- Clinical Reviewer (DVRPA/VCTB)
- Product Reviewer (DVRPA/DVP or DBPAP)
- Statistical Reviewer (OBE/DS)
- Other (if necessary):
  - Toxicologist
  - Consult clinical specialist based on indication
  - Consult reviewer from other centers for combination products or for unique aspects of IND, e.g., diagnostic assays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IND Content & Format [21 CFR 312.23]

- Cover Sheet (Form 1571)
- Table of Contents
- Introductory Statement & General Investigational Plan
- Investigator's Brochure
- Protocol
- CMC Information
- Pharmacology & Toxicology Information
- Previous Human Experience
- Additional information

Clinical Protocol Elements [21 CFR 312.23 (a)(6)(iii)]

- Objectives & Purpose
- Investigator Info (Form 1572)
- Inclusion/Exclusion / # Subjects
- Study Design
- Dose & Schedule
- Monitoring to Meet Objectives
- Monitoring to Minimize Risks

[See also ICH E6 (Good Clinical Practice)]

Helpful Hints for IND Original Submissions:

- Paginate the entire submission.
- Contact DVRPA prior to submission:
  - Heads up
  - Question need for extra copies
- Number and title protocol.
- Include consent form, case report form, & patient diary with protocol.
- Tabulate supportive preclinical & previous clinical data for easy comparison, as well as provide text summaries.
- Provide reprints of key referenced publications and draft manuscripts.
- Provide safety data from previous clinical studies (vs. describe as “well tolerated”).
- Provide bovine-source documentation, if applicable.

Clinical Hold
[21 CFR 312.42]

- "…an order by FDA to the sponsor to delay a proposed clinical investigation or to suspend an ongoing investigation."
- "…may apply to one or more of the investigations covered by an IND."
- For a proposed study, subjects may not receive the study vaccine.
- For an ongoing study, no new subjects may be recruited and given the vaccine; patients already in the study should receive no additional doses of vaccine.

Grounds for Clinical Hold
[21 CFR 312.42 (b)(1) &(2)]

- **For Phase 1, 2 or 3 Studies:**
  - **Subjects are or would be exposed to an unreasonable & significant risk of illness or injury.**
  - **The clinical investigators are not qualified.**
  - **IB is misleading, erroneous, or materially incomplete.**
  - **Does not contain sufficient information to assess the risk to subjects of the proposed studies.**
- **For Phase 2 or 3 Studies only:**
  - **Protocol is clearly deficient in design to meet its stated objectives.**

OVRR Clinical Hold Policy and Practice

- Notify sponsor of clinical hold decision by telephone on or before the 30-day decision date.
- Issue a clinical hold letter within 30 days of initial sponsor notification of the clinical hold.
- Issue a separate advice/information request (AI) letter with non-hold issues.

IND Review & Correspondence Clocks

- An IND goes into effect 30 days after FDA receives the IND, unless FDA notifies the sponsor that the IND has been placed on clinical hold. [21 CFR 312.40 (b)(1)].
- If a sponsor submits a complete response to the issues identified in the clinical hold order, FDA shall respond in writing within 30 days to maintain or remove the hold.
- A sponsor may not proceed with a study until notification from FDA that the hold has been lifted.

Types of IND Amendments

- Protocol
- Information
- Safety
- Annual Reports

IND Amendments

- Protocol Amendments [21 CFR 312.30]:
  - New Protocol
  - Changes in a Protocol
    - Affects safety of subjects
    - Scope of investigation
    - Scientific quality of study
    - New investigator
- Information Amendments [21 CFR 312.31]
  - (e.g., product changes, response to information request)

- **Safety Reports [21 CFR 312.32]**
  - **Written report**
    - **Within 15 days of sponsor's initial receipt of info.**
    - **Serious and unexpected adverse experience**
    - **Animal data that suggest a significant risk**
    - **Identify all previous reports of experience**
  - **Telephone or Fax**
    - **Within 7 days of sponsor's initial receipt of info.**
    - **Unexpected fatal or life-threatening**
  - **FDA may request a different format or frequency**
  - **Disclaimer – submission of report doesn't reflect causation**

- **Annual Reports [21 CFR 312.33]**
  - Individual study information
    - Title, purpose, population, ongoing or completed
    - # subjects planned, enrolled, demographics, drop-outs
    - Any available study results
  - Summary Information from previous year
    - Most frequent & most serious AEs by body system
    - All IND safety reports submitted
    - Deaths and causes
    - Drop-outs due to AEs whether or not related
    - Description of new data which contributes to understanding the vaccine's actions (e.g., dose resposne, immunogenicity)
    - Preclinical studies – ongoing or completed
    - Significant CMC changes
    - General investigational plan for coming year
    - IB revisions, if applicable.
    - Significant Phase 1 protocol changes not previously noted
    - Significant foreign marketing developments
    - Log of any outstanding IND business

Common Pitfalls of Vaccine IND Submissions

- **Manufacturing**
  - **Insufficient information on sources, manufacturing processes, facilities, stability, storage, etc.**
  - **Potentially toxic substances: validation of removal or assay for residual component**
  - **Adventitious agents: inadequate testing or inadequate information on source materials**
- **Lot Information**
  - **Lot release test results lacking**
  - **Lots not clearly identified**
  - **Data not summarized & tabulated (i.e., stage of manufacture, test, acceptance criteria, test result)**

Common Pitfalls of Vaccine IND Submissions

- **Preclinical Issues:**
  - Lack of data concerning:
    - Pyrogenicity
    - Attenuation (live organisms)
    - Inactivation/reversion
    - Potency (e.g., immunogenicity)
    - Adjuvant justification
  - GLP safety study (Phase 1) for a novel product
  - Experimental details lacking
    - Need information on lot, dose, route, assays to evaluate immune response, etc.
  - Data to support dose proposed for clinical trial
  - Pre-IND Meeting with CBER not held

Common Pitfalls of Vaccine IND Submissions

- **Protocol Issues:**
  - **Inadequate stopping rules for individuals and entire study cohort.**
  - **No or inadequate safety follow-up.**
  - **Subject diary and case report form for safety monitoring (local & systemic) not submitted.**
  - **No detail on assays to evaluate immune response.**
  - **Poorly defined end point(s) & case definition.**
  - **Inadequate or no statistical analysis plan.**
  - **Inconsistencies within protocol and between protocol and other documents.**

Available CBER Guidance

- Guidance for Industry
- Guidelines
- Points to Consider
- Federal Register Notices
- ICH Topics & Guidelines
- Reviewers' Guides
- CBER SOPPs

CBER Guidance

- **Web: www.fda.gov/cber/reading.htm**
- **Email: OCTMA@CBER.FDA.GOV**
- **Fax: 1-888-CBER-FAX**
- **Phone**

  DVRPA: 301- 827-3070

  OCTMA: 301- 827-1800

Additional References

- CBER SOPPS: http://www.fda.gov/cber/regsopp/regsopp.htmBSE
- BSE Issues including estimating risk: http://www.fda.gov/cber/bse/bse.htm
- Goldenthal KL, et al. Preventive HIV-1 Vaccine Clinical Trials: A regulatory perspective. AIDS Res Hum Retro Suppl 3:S333-40, 1998
- Baylor N, Midthun K: Regulation & Testing of Vaccines. Vaccines 4th ed, 2004, WB, Saunders
- Shapiro SZ. The HIV/AIDS vaccine researchers' orientation to the process of preparing a US FDA application for an investigational new drug (IND): what it is all about and how you start by preparing for your pre-IND meeting. Vaccine 20(2002): 1261-1280.

Summary

- The regulation of vaccines is based on sound science, law and public health impact.
- Early and open communication with CBER may facilitate vaccine development and resolution of issues.
- Pre-IND meetings are strongly recommended.
- CBER advice is based on regulatory requirements, as well as experience.
- Many pitfalls can be avoided if sponsors use available guidance and other resources, ask questions, and consider CBER advice.

Special Thanks to…

- Karen Goldenthal, M.D.
- Donna Chandler, Ph.D.
- Paul Richman, Ph.D.
- Julianne Clifford, Ph.D.
- Jon Daugherty, Ph.D.